Systemic and Coronary Hemodynamic Effects of Triamterene (2, 4, 7 Triamino-6-Phenyl Pteridine)*† (27410)

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Triamterene (2,4,7 triamino-6-phenyl pteridine, SKF 8542) (Fig. 1) is a compound recently described chemically and pharmacologically(1) and tried clinically as a diuretic (2,3,4). The agent has shown considerable therapeutic promise in heart failure, nephrosis and cirrhosis, particularly when aldosterone appears to be active(3,4). Since its use is potentially important in treatment of cardiovascular failure and hypertension(3) it seemed of interest to establish the hemodynamic effects of the compound in man. The agent is active when given by mouth and appears in the urine within 15-30 minutes after oral administration(3) suggesting this route as logical for testing.

Material and methods. Hemodynamic studies were done on fasting hospitalized subjects. The patients were selected from the hospital medical wards and had a variety of non-cardiovascular medical problems. Two cardiac catheters were inserted through either the same median antecubital vein or closely adjacent veins exposed through the same small incision in the antecubital region. One catheter was manipulated under fluoroscopic control into the pulmonary artery and the other into the coronary sinus. Cardiac output was determined by the Fick principle, and coronary blood flow by the nitrous oxide saturation method utilizing a blood-heart partition coefficient of one. Arterial specimens were obtained directly through an indwelling Cournand needle, placed in the femoral artery. Blood gas analyses were done by the Van Slyke-Neill method. Expired air was collected in a Tissot spirometer and analyzed for oxygen and carbon dioxide by the Scholander apparatus. Pressures were determined by Statham strain gauges. Right and left ventricular work was calculated without subtracting the left or right atrial pressure from the appropriate arterial mean pressure.

After control observations on cardiac output and coronary blood flow had been made, the subjects were gvien 300 mg of SKF 8542 orally. They then lay on the fluoroscopy table for a period of 1 hour when cardiac output and coronary blood flow were determined again. The original series began with 9 subjects. The first of these was subsequently eliminated from the series because the dose was 150 mg, whereas the dose in the rest of the series was 300 mg. Another subject was eliminated from the totals because hyperventilation associated with a considerable increase in body oxygen consumption occurred during the second determination of cardiac output. Hence the summary presents data on 7 completed studies.

Results. The results summarized in Table I indicate that one hour after oral administration of 300 mg of triamterene to these human subjects there was no change in heart rate nor in mean systemic or pulmonary arterial blood pressure. The mean coronary sinus pressure, which is taken as an index of central venous pressure, was significantly reduced. The minute volume of respiration was unchanged as were body oxygen consumption and respiratory quotient. Arterial

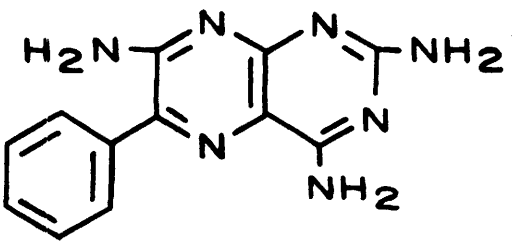

FIG. 1. SKF 8542.

* This study was supported in part by grants from Nat. Heart Inst., U.S.P.H.S., Wisconsin Heart Assn., and Wisconsin Alumni Research Foundation.

† Triamterene was supplied by the courtesy of Smith Kline & French Laboratories, Philadelphia, Pa.

TABLE I. The Systemic and Coronary Hemodynamic Effects of Triamterene.

	Before	After	% change	P value <
Heart rate	74	71	− 4.1	.3
Mean systemic arterial blood pressure (mm Hg)	95	97	+ 2.1	.4
" pulmonary " " " "	16	15	− 6.3	.5
" coronary sinus " " " "	4.6	3.6	−21.7	.01
Oxygen consumption/M^2 surface area	138	139	+ 0.72	.4
Body respiratory quotient	.82	.85	+ 3.7	.7
Arterial-coronary sinus O_2 diff. (ml/100 ml of blood)	13.0	13.2	+ 1.5	.01
Cardiac index (l/min./M^2)	3.7	3.1	−16.2	.02
Stroke index (cc/M^2)	49	44	−10.2	.05
Total peripheral resistance (cgs units)	1185	1411	+19.1	.01
Coronary blood flow (ml/100 g/min.)	73	78	+ 6.8	.2
Index of efficiency (LVW ÷ $CMRO_2$)	.52	.43	−17.3	.01

oxygen content remained unchanged, but a significant widening of arterio-venous oxygen and carbon dioxide difference occurred. Coronary sinus oxygen and carbon dioxide content remained unchanged. Neither arterial hemoglobin nor hematocrit changed, nor did the pH in the femoral arterial or coronary sinus blood.

The cardiac index was decreased significantly. Left ventricular work was reduced variably but not significantly, whereas the reduction in right ventricular work was greater and was statistically significant. Although total peripheral resistance was significantly increased, total pulmonary resistance increased slightly and variably and the change was not significant. Neither coronary vascular resistance nor myocardial oxygen consumption changed and the cardiac respiratory quotient was unaltered. As a manifestation of the reduced left ventricular work with maintained cardiac oxygen consumption, the calculated index of efficiency decreased significantly.

Discussion. The hemodynamic effects of acute administration of Triamterene(2,4,7 triamino-6-phenyl pteridine) are not striking, and recall both qualitatively and quantitatively the reduction in cardiac output produced by acute administration of chlorothiazide(5,6,7,8). Exhibition of both of these agents is accompanied by a decrease in central venous pressure and cardiac output(5,8) whereas coronary flow is not significantly changed(8). Because of the decreased left ventricular work in the presence of sustained myocardial oxygen consumption, calculated cardiac efficiency is slightly reduced(8). This reduction in efficiency is an almost invariable accompaniment of decreased cardiac output (9), especially when stroke index and stroke work index are reduced. Whereas the reduction in cardiac output is certainly of borderline clinical significance, it is of considerable theoretical interest, especially when coupled with the fact that the total peripheral vascular resistance increased significantly. With chlorothiazide, acute administration to hypertensive subjects is associated with a decrease in arterial pressure, but accompanied by an incerase in peripheral vascular resistance(5,6,7,8). However, with more prolonged administration, the cardiac output returns more nearly to normal, and peripheral vascular resistance eventually decreases(7). Information concerning the hemodynamic effects of SKF 8542 in treatment of hypertension are not yet available, but preliminary trials have indicated some decrease in arterial pressure may occur(3).

Conclusions. 1. The acute hemodynamic effects of oral administration of 300 mg of triamterene are reported in a series of 7 normotensive human subjects. 2. Administration of the agent was associated with a decrease in cardiac output, accompanied by a reduction in central venous pressure, insignificantly diminished left ventricular work, and an increase in peripheral vascular resistance. 3. Coronary blood flow was unchanged and myocardial oxygen consumption maintained at the control level whereas calculated cardiac efficiency was reduced.

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Received February 5, 1962. P.S.E.B.M., 1962, v110.

Immunoassay of Insulin Using a Two-Antibody System.* (27411)

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Immunoassay of insulin utilizing lysis of sensitized RBC(1), salt precipitation(2), and paper electrophoresis(3) has been reported.

It has been shown that I^{131}-insulin, which is bound *in vitro* by serum obtained from insulin resistant patients, can be quantitatively precipitated by an antibody to human gamma globulin(4). This suggested the possibility of using a similar system for insulin assay. The present paper describes a simple, rapid, and versatile assay method permitting large numbers of determinations to be carried out with high precision and great sensitivity.

The reaction consists of two steps. In the first, insulin forms a soluble complex with its specific antibody, which is obtained from immunized guinea pigs (AIS-GP). In the second, this soluble complex is precipitated by antibody to guinea pig serum, which is obtained from rabbits (AGPS-R).

The overall reaction is dependent upon the concentrations of the various reactants used, *i.e.*, AIS-GP, AGPS-R, and insulin. Using tracer amounts of I^{131}-insulin, the percent of radioactivity in the precipitate is dependent upon the total amount of insulin in the reaction mixture; as increasing amounts of unlabeled insulin are added, the percent of I^{131}-insulin in the precipitate is decreased correspondingly.

* This investigation was supported by research grants from Nat. Inst. of Arthritis and Metab. Dis., and from Division of General Medical Sciences, N.I.H., U.S P.H.S.

Materials. The AIS-GP used was obtained from guinea pigs immunized to insulin (Iletin, Lilly) using a Freund adjuvant(5,6). The AGPS-R was purchased from Sylvanna Chemical Co. Special preparations of I^{131}-insulin having specific activities greater than 200 mc/mg were supplied by Drs. J. L. Izzo and W. F. Bale.† A commercially available product of lower specific activity was also used.‡ All dilutions of serums and standards were made in 5% bovine serum albumin-borate buffer, at pH 8.5, containing 1:10,000 merthiolate (5% BSA).

Method. The following procedure was used to obtain the results shown in Fig. 1. The components were added to a 12 × 75 mm tube in the order indicated.

Step 1: (a) 0.5 ml of unlabeled human insulin solution containing 0.5 μU to 64 μU *i.e.*, 1-128 μU per ml. (b) 0.1 ml of tracer I^{131}-insulin solution containing 10 μU (25,000 cpm). (c) 0.1 ml of 1:10,000 dilution of AIS-GP. This reaction mixture was refrigerated (4°C) overnight (26 hours).

Step 2: The following were added: (d) 0.1 ml AGPS-R. (e) 0.1 ml 1:200 dilution of normal guinea pig serum (NGPS). The tubes were refrigerated for 2 hours and then centrifuged at 2000 rpm for 20 min. at room temperature. The supernatant was decanted. The precipitate was washed with 0.5 ml 1%

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‡ I^{131}-insulin, sp. ac. 20-30 mc/mg, Abbott Pharmaceutical Co.